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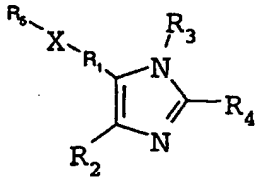

(I)

(57) Abstract

Novel 4– phenyl– 5–(2– aryl–X)– 4–pyrimidinyl–, 4– phenyl–5– (2–cycloalkyl– X)–4–pyrimidinyl–, 4– phenyl–5– (–aralkyl–X)–4–pyrimidinyl– or 4–phenyl– 5–(2–cycloalkylalkyl– X)–4–pyrimidinyl– imidazoles, in which the 5– pyrimidinyl substituent is aryl, cycloalkyl, aralkyl or cycloalkylalkyl substituted directly via a heteroatom X selected from N, O or S, and pharmaceutically–acceptable and –cleavable esters thereof and acid addition salts thereof are provided, in particular compounds of formula (I), wherein the symbols are as defined, which are MAP kinase inhibitors, useful pharmaceutically for treating TNFα and IL–1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis.

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ANTI-INFLAMMATORY 4-PHENYL-5-PYRIMIDINYL-IMIDAZOLES

This invention relates to 4-phenyl-5-[(2-substituted)-4-pyrimidinyl]-1-H-imidazoles which are the tautomeres of 5-phenyl-4-[(2-substituted)-4-pyrimidinyl]-1-H-imidazoles and to their use for treating TNFα and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis. Both tautomers represent the same structure; their nomenclature may be used interchangeably.

Accordingly the present invention provides novel 4-phenyl-5-[(2-aryl-X)-4-pyrimidinyl]-, 4-phenyl-5-[(2-cycloalkyl-X)-4-pyrimidinyl]-, 4-phenyl-5-(2-aralkyl-X)-4-pyrimidinyl- or 4-phenyl-5-[(2-cycloalkylalkyl-X)-4-pyrimidinyl] -imidazoles, in which X is a heteroatom selected from N, O or S, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

The 5-pyrimidinyl substituent is aryl-, cycloalkyl-, aralkyl- or cycloalkylalkyl-substituted directly via a heteroatom selected from N, O or S, i.e. the aryl, cycloalkyl, aralkyl or cycloalkylalkyl substituent and the pyrimidinyl ring are linked by a single atom which is N, O or S. Preferably the heteroatom is optionally substituted N, more preferably -NH-.

The aryl or aralkyl substituent may comprise a carboaryl substituent or a heteroaryl substituent; for instance, phenyl, benzyl, phenylethyl, 4-pyridylmethyl, naphthyl (e.g. naphth-1-yl or naphth-2-yl), pyridyl (e.g. 4-pyridyl), pyrimidinyl, quinazolinyl (e.g. quinazolin-4-yl), quinolinyl, isoquinolinyl, imidazolinyl (e.g. 2- or 3-imidazolyl) or benzamidazolinyl (e.g. 2-benzamidazolyl). The cycloalkyl or cycloalkylalkyl substituent may comprise a C_3 to C_{12} cycloalkyl ring, e.g. a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl ring. The aryl, cycloalkyl, aralkyl and cycloalkylalkyl substituents may be optionally substituted, e.g. by up to 3 substituents selected from alkyl, halogen, halo-substitued-alkyl, hydroxy, alkoxy, alkylthio, optionally substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom (e.g. O, S or N). Preferably the aryl or aralkyl substituent on the 5-pyrimidinyl substituent is benzyl, phenylethyl, 4-pyridylmethyl or phenyl, optionally substituted, preferably in the meta and/or para positions, by halogen, C_{1-10}alkyl, C_{1-}

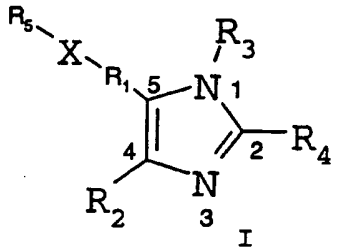
$_{10}$alkoxy, hydroxy, halo-substitued C_{1-10}alkyl (e.g. trifluoromethyl), or optionally substituted amino.

The 4-phenyl substituent may be unsubstituted, though is preferably substituted by one or more substituents, each of which may be independently selected from halo, cyano, amido, thioamido, carboxylate (including thiocarboxylate and esters of both of these), optionally substiutedC_{0-1}alkyl optionally substituted carbonyl or thiocarbonyl (i.e. both aldehyde and ketone), alkoxy or thioalkoxy, optionally substituted alkyl, optionally substituted oxycarbonyl or amino-carbonyl (including thio analogues thereof), (optionally substituted)-amino or -aminomethyl, optionally substituted alkylamino-carbonyl or -thiocarbonyl, optionally substituted amino-sulphinyl or -sulphonyl optionally substituted by amino. Preferably the 4-phenyl has up to 3 substituents and preferably these are halo or halo-containing substituents, e.g. the 4-phenyl substituent is 2, 4, 5 trihalo-substituted phen-1-yl or especially 4-halo-, 3-trifluoromethyl, 3-chloro, or 3,4-difluoro substituted.

The C-2 and N1 atoms of the of the imidazole ring may also be substituted, conveniently by substituents such as those described at equivalent positions in WO 95/03297, WO 97/25048, WO 97/12876 or WO 99/01499. The numbering of the atoms of the imidazole ring is shown below in Figure I.

Above and elsewhere in the present description the terms halo or halogen denote I, Br, Cl or F, preferably F.

In particular embodiments the invention provides a compound of formula I



I

wherein

R_1 is pyrimidinyl;

X is $-NR_6-Y-$, -O- or -S-,

where R_6 is H, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, C_7-C_{19}aralkyl or C_4-C_{19}heteroaralkyl, and -Y- is C_{1-4}alkylene or a direct bond ;

R_2 is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF_3,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C_{1-4}alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C_{1-4}alkyl C_{1-4}alkylcarbonyl or C_{1-4}alkylthiocarbonyl substitued,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C_{1-10}alkoxy, C_{2-10}alkenoxy, C_{2-10}alkynoxy, C_{3-7}cyclalkoxy, C_{5-7}cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester,

optionally mono- or di-C_{1-4}alkyl-substituted-C_{0-1}alkyl optionally C_{1-4}alkyl- or C_{3-5} cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted-C_{1-4}alkoxy, C_{2-4}alkenoxy, C_{2-4}alkynoxy, C_{3-5}cycloalkoxy or C_{3-5}cyclothioalkoxy,

optionally halo substituted C_{1-4} alkyl,

oxycarbonyl or optionally N-C_{1-4}alkyl-substituted aminocarbonyl both of which are optionally C_{1-4}alkyl or C_{3-5}cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di-C_{1-4}alkyl-substituted-C_{0-1}alkylamine which is optionally mono-or di-N-C_{1-4} alkyl substituted,

optionally mono- or di-C_{1-4}alkyl-substituted-C_{0-1}alkyl optionally N-C_{1-4}alkyl-substituted amino-carbonyl or -thiocarbonyl,

optionally N-C_{1-4}alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C_{1-4}alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_{1-4}alkyl C_{1-4}alkylcarbonyl or C_{1-4}alkylthiocarbonyl substituted, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C_{1-4}alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl,

optionally mono- or di-N-C_{1-4}alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_{1-4}alkyl C_{1-4}alkylcarbonyl or C_{1-4}alkylthiocarbonyl substituted;

R_3 is hydrogen,

heterocyclyl,

heterocyclylC_{1-10}alkyl,

optionally halo substituted C_{1-10}alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10}alkyl, heteroaryl, or heteroarylC_{1-10}alkyl,

optionally mono-or di-C_{1-4}alkyl-substitutedC_{0-10}alkyl-oxycarbonyl or -oxythiocarbonyl optionally substituted by C_{1-10}alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10}alkyl, or

optionally mono-or di-C_{1-4}alkyl-substitutedC_{1-10}alkyl

-cyano,

-nitro,

-hydroxy, -C_{1-10}alkoxy, -C_{3-7}cycloalkoxy, -heterocycloxy, -heterocyclylC_{1-10}alkoxy, -aryloxy, -arylC_{1-10}alkoxy, -heteroaryloxy, -heteroarylC_{1-10}alkoxy (and thio oxy analogues thereof),

optionally substituted amino, carboxylate, thiocarboxylate, carbonyl or thiocarbonyl, sulphinyl or sulphonyl;

R_4 is H, or C_{1-10}alkyl, C_{3-10}cycloalkyl, C_{3-18}heterocycloalkyl, C_{6-18}aryl, or C_{3-18}heteroaryl all optionally substituted by up to 4 substituents separately selected from alkyl, halogen, halo-substitued-alkyl, hydroxy, alkoxy, alkylthio, or optionally substituted amino;

R_5 is C_6-C_{18}aryl, C_3-C_{18}heteroaryl, or C_3-C_{12}cycloalkyl optionally substituted by up to 3 substituents separately selected from alkyl, halogen, halo-substitued-alkyl, hydroxy, alkoxy, alkylthio, optionally substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

R_1 is preferably 4-pyrimidinyl.

When R_4 is alkyl it is C_1-C_{10}alkyl, preferably C_1-C_6alkyl, optionally substituted, preferably with one or two substituents separately selected from hydroxy, C_1-$_6$alkoxy or amino.

When R_4 is aryl or heteroaryl either of which is optionally substituted by up to 4 substituents, R_4 may comprise one of the customary aryl or heteroaryl substituents in the art and may be substituted as is customary in the art; for instance as defined for the substituent R_3 of of WO 93/03297.

When R_4 is cycloalkyl it is preferably C_3-C_8, especially C_5-C_6cycloalkyl (e.g. cyclohexyl), optionally substituted, preferably with up to 2 substituents separately selected from alkyl, halogen, hydroxy, alkoxy, or amino.

When R_4 is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, optionally substituted, e.g. by up to 2 substituents, selected from halogen, hydroxy, alkoxy, or amino.

When R_5 is aryl it is preferably phenyl. When R_5 is cycloalkyl, it is preferably C_3-C_7 cycloalkyl, e.g. cyclopropyl, cyclopently, cyclohexyl or cycloheptyl. R_5 may be unsubstituted or substituted, preferably mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen, C_{1-10}alkyl, halo-substitued C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy or -NR_7R_8, where R_7 and R_8 are idependently H, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}heteroaryl, C_{7-11}aralkyl or C_{7-11}heteroaralkyl.

When -Y- is C_1-C_4 alkylene, it is preferably C_1-C_2 alkylene, and is optionally substituted, e.g. by C_1-C_4alkyl (e.g. methyl), halogen, hydroxy, alkoxy, or amino.

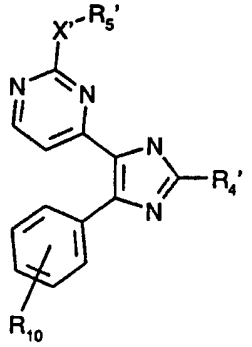
Preferably R_2 is phenyl substituted, preferably mono-substituted, by halogen, e.g. 4-fluorophen-1-yl, or 3-CF_3, 3-Cl, or 3,4-difluoro substituted.

Preferably R_3 is H.

Preferably R_4 is H or C_{1-6} lower alkyl, 1-hydroxyC_{1-10}alkyl, 1-C_{1-6}alkoxyC_{1-10}alkyl, 1-aminoC_{1-10}alkyl, 1-hydroxyC_{3-10}cycloalkyl, 1-C_{1-6}alkoxyC_{3-10}cycloalkyl, 1-aminoC_{3-10}cycloalkyl, 1-hydroxyC_{3-18}heterocycloalkyl, or 1-C_{1-6}alkoxyC_{3-18}heterocycloalkyl.

Preferably X is -NH-Y'-, -O- or -S-, where Y' is -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$- or a direct bond

Thus in preferred embodiments the invention provides a compound of formula I'



I'

wherein

R_5' is phenyl or C_3-C_7cycloalkyl each of which is optionally mono-substituted by halogen, C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, trihalomethyl or -NR_7R_8, where R_7 and R_8 are idependently H, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}heteroaryl, C_{7-11}aralkyl or C_{7-11}heteroaralkyl;

R_{10} is halogen, cyano, amido, thioamido, amino or C_{1-6}alkyl;

R_4' is H, C_{1-6}alkyl, 1-hydroxyC_{1-10}alkyl, 1-C_{1-6}alkoxyC_{1-10}alkyl, 1-aminoC_{1-10}alkyl, 1-hydroxyC_{3-10}cycloalkyl, 1-C_{1-6}alkoxyC_{3-10}cycloalkyl, 1-aminoC_{3-10}cycloalkyl, 1-hydroxyC_{3-18}heterocycloalkyl, or 1-C_{1-6}alkoxyC_{3-18}heterocycloalkyl, and

X' is -NH-Y'-, -O- or -S-, where Y' is -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$- or a direct bond,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

In the present description the terms such as "C_{3-18}heteroaryl, C_{4-19}heteroaralkyl and C_{3-18}heterocycloalkyl" denote heteroaryl, heteroaralkyl or heterocycloalkyl substituents comprising at least 3 ring atoms, at least one of which is a hetero atom, e.g.N, O or S, and which in the case of C_{4-19}heteroaralkyl groups are attached via an alkylene moiety comprising at least 1 carbon atom.

Preferably R_5' is monosubstituted by halogen, C_{1-4}alkyl (e.g. methyl), C_{1-4}alkoxy (e.g. methoxy), hydroxy or CF_3. For instance, when R_5' is C_{3-18}heterocycloalkyl, eg. piperidinyl, it may be substituted, preferably at the hetero atom thereof, e.g. as N-C_{1-4}alkyl-piperidinyl

Preferably R_{10} is halogen.

Preferably X' is -NH-, -NH-Y'- or -O-.

The Invention includes the following compounds:
4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(2-(3-bromophenylamino)-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(2-(3-hydroxyphenylamino)-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(2-(4-bromophenylamino)-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(2-(3-methoxyphenylamino)-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(2-(3-methylphenylamino)-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(2-(3-trifluoromethylphenylamino)-4-pyrimidinyl)imidazole;
4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-2-tert.butylimidazole;
4-(4-Fluorophenyl)-5-(2-(3-fluorophenyloxy)-4-pyrimidinyl)imidazole;
2-(1-Aminocyclohexyl)-4-(4-fluorophenyl)-5-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole;
5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole;
5-(4-Fluorophenyl)-2-(1-aminocyclohexyl)-4-(2-(3-methylphenyl-1-amino)-4-pyrimidinyl)-1-H-imidazole;
5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)-ethyl]-4-(2-(R)-1-phenylethyl amino-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)ethyl]-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)-ethyl]-4-(2-cyclohexylamino-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-[(1-amino-1-methyl)-ethyl]-4-(2-cyclopropyl methylamino-4-pyrimidinyl)-1-H-imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclohexylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclopropylmethylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cycloheptylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclopropylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-cyclopentylamino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-ethylpiperidinyl)-4-(2-(S)-1-phenylethyl amino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-hydroxy-4-ethylpiperidinyl)-4-(2-cyclohexylamino-4-pyrimidinyl)-1-H- imidazole;

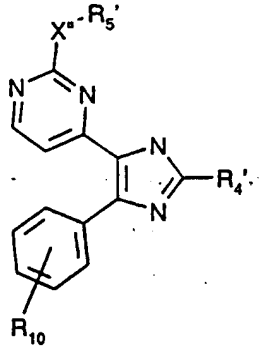
5-(4-Fluorophenyl)-2-(1-hydroxy-4-ethylpiperidinyl)-4-(2-cyclpropylmethyl amino-4-pyrimidinyl)-1-H- imidazole;

5-(4-Fluorophenyl)-2-(1-n-butyloxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole, and

5-(4-Fluorophenyl)-2-(1-n-butyloxy-4-methylpiperidinyl)-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole.

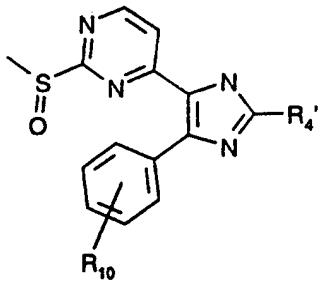
The novel imidazoles of the invention, in particular the compounds of formulae I and I' and the specific compounds listed above are hereinafter referred to "Agents of the Invention".

Agents of the Invention of formula I''



I''

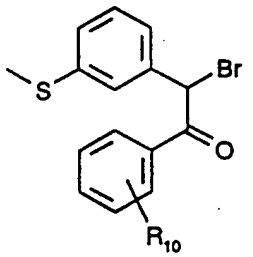
wherein R_4', R_5' and R_{10} are as previously defined and X'' is -NH- or -O-, may be prepared by reacting the corresponding precursor compound of formula II



II

wherein R_4' and R_{10} are as previously defined, with the corresponding R_5'-NH_2 or R_5'-OH derivative. For example, the reaction may be carried out by refluxing the reactants in an organic solvent, e.g. dichloroethane, e.g. in the presence of diethoxytrifluoroborane.

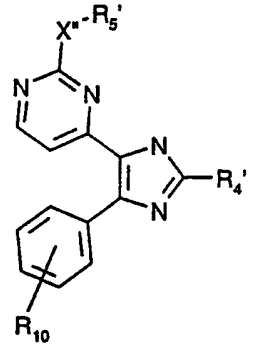
The precursor compound of formula II may be prepared by controlled oxidation of the corresponding 5(2-methylthio-4-pyrimidinyl)-4-phenylimidazole, e.g. employing an oxidising agent such as mCPBA (meta chloroperbenzoic acid), conveniently in an organic solvent such as methylene chloride. The corresponding 5(2-methylthio-4-pyrimidinyl)-4-phenylimidazole compound may be prepared by contacting the corresponding acetophenone precursor compound of formula III



III

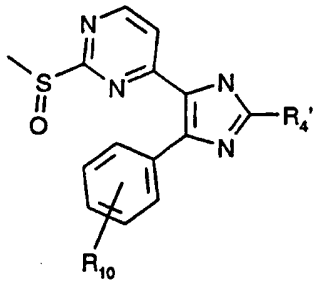
wherein R_{10} is as defined above, with a mixture of formic acid formamide and ammonium formiate at elevated temperature, e.g. at a temperature of up to about 190°C. The compound of formula III may be prepared by bromination of the corresponding 2-(2-methylthio-4-pyrimidinyl)acetophenone. The 2-(2-methylthio-4-pyrimidinyl)acetophenone precursor may be prepared by reacting the corresponding N-methoxy-N-methylbenzamide with 4-methyl-2-(methylthio)pyrimidine, e.g. in a THF containing organic solvent with cooling.

Thus in a further aspect the invention includes a process for the preparation of a compound of formula I''



I''

wherein R_4', R_5' and R_{10} are as previously defined and X'' is -NH- or -O-, which comprises reacting the corresponding precursor compound of formula II



II

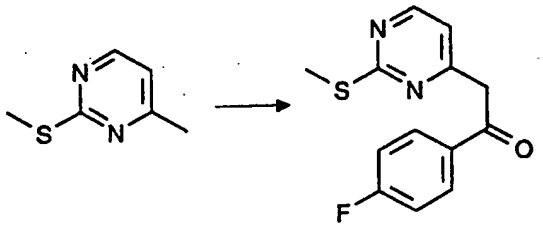
wherein R_4' and R_{10} are as previously defined, with the corresponding R_5'-NH_2 or R_5'-OH derivative.

The synthesis of Agents of the Invention is further described in the following Examples.

EXAMPLES

Example 1: 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-1-H-imidazole

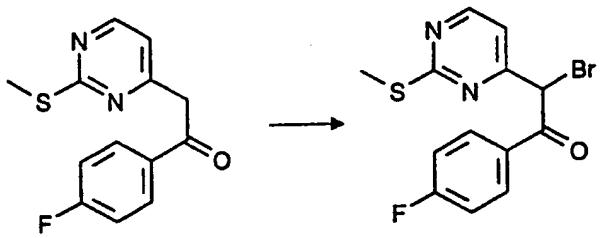
a) 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone



n-BuLi (10 ml of a 1.6 M solution in hexane; 12 mmol) is added at -78°C to a solution of diisopropylamine (2.48 ml; 17 mmol) in THF (15 ml) and stirred for 5 min. 4-Methyl-2-(methylthio)pyrimidine (2g; 14.5 mmol) dissolved in THF (2 ml) is added dropwise and stirred for 30 min at -78 C. 4-Fluoro-N-methoxy-N-methylbenzamide (2.66 g; 14.5 mmol) is dissolved in THF (3 ml) and added slowly to the reaction mixture. The mixture is warmed to r.t. within 45 min. and poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield 2.5 g (65%) of yellow crystals after recrystallisation from tert.butyl methyl ether/hexane.

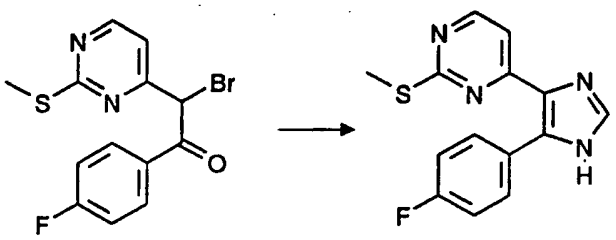
1H-NMR (200 MHz $CDCl_3$): 3.00 (s, 3H); 6.30 (s, 1H; vinyl-H of enol); 7.00 (d, 1H); 7.50 (dd, 2H); 8.20 (dd, 2H); 8.7 (d, 2H). Due to pH-dependent keto-enol tautomery, signals may be duplicated.

b) 4-Fluoro-2-bromo -2-(2-methylthio-4-pyrimidinyl)acetophenone



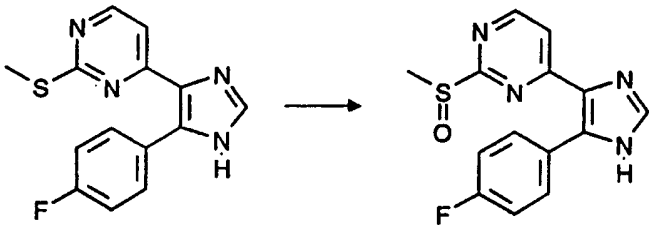
Bromine (1.22g; 7.6 mmol) in acetic acid (5.6 ml) is added to a solution of 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone (2g; 7.6 mmol) in acetic acid (40 ml). The initially thick precipitate is almost dissolved after 20 min., filtered and the filtrate evaporated to dryness. The residue is taken up in a saturated solution of $NaHCO_3$ and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield 2.6 g (100%) of a brown oil, which is used in the next step without purification.

c) 4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidinyl)-1-H-imidazole



4-Fluoro-2-bromo -2-(2-methylthio-4-pyrimidinyl)acetophenone (0.2 g; 0.58 mmol) is dissolved in formic acid (2.6 ml), formamide (2.1 ml) and ammonium formate (2.6g) added and heated at 190 C for 20 min. The mixture is poured on water (100 ml), filtered, and the filtrate adjusted to pH ~10 with a saturated solution of Na_2CO_3. A yellow precipitate is formed and yielded after washing with water and drying at high vacuum the title compound (63 mg; 38%).
1H-NMR (360 MHz DMSO-d6): 2.18 (s, 3H); 7.28 (dd, 2H); 7.45-7.55 (bs, 1H); 7.65 (dd, 2H); 7.90 (s, 1H); 8.50 (d, 1H); 12.85 (bs, 1H).
FAB-MS (m/z): 287 (MH+).

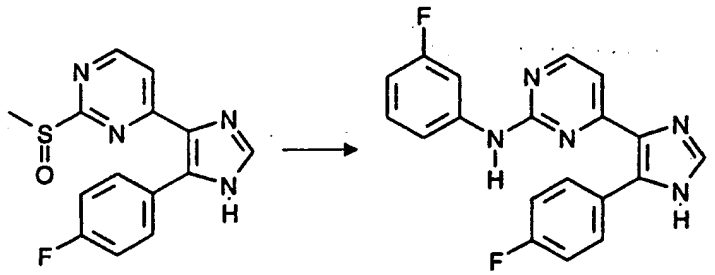
d) 4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-1-H-imidazole



4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidinyl)imidazole (0.1 g; 0.35 mmol) in methylene chloride (1 ml) is stirred and cooled to 5-10 C and mCPBA (55%, 0.33 g; 1.4 mmol) in methylene chloride (3 ml) added. The yellow, turbid mixture clears and becomes almost colorless and is

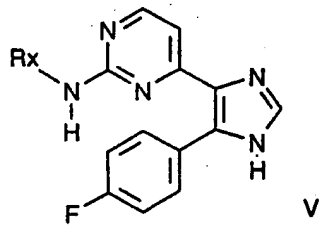
warmed up to r.t. A precipitate formed after ~1.5 hrs and is stirred for another 6 hrs. The precipitate is filtered off, washed with ether and yields the title compound (77 mg; 70%).
1H-NMR (360 MHz DMSO-d6): 3.05 (s, 3H); 7.28 (dd, 2H); 7.72 (dd, 2H); 8.00 (s, 1H); 8.05-8.20 (bs, 1H); 8.92 (d, 2H); 13.00 (bs, 1H).

e) 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-1-H-imidazole



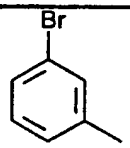
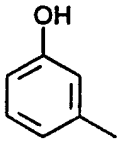
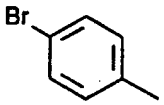
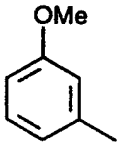
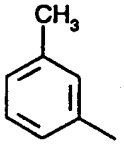
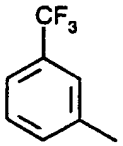
4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole (0.05 g, 0.16 mmol) is dissolved in 1,2-dichloroethane (2 ml), 3-fluoroaniline (0.5 ml, 5.2 mmol) and $BF_3.OEt_2$ (0.02 ml; 0.16 mmol) added and the reaction mixture refluxed for 3.5 hrs. The mixture is taken up in 1N Na_2CO_3 and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield a brown oil (520 mg), which is purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_3 conc 97.5/2.5/0.25) and gives the title compound (10 mg; 18%) as off-white crystals.
1H-NMR (400 MHz DMSO-d6, 120 C): 6.32 (dt, 1H); 7.02-7.08 (m, 3H); 7.15 (dd, 1H); 7.22 (td, 1H); 7.82 (dd, 2H); 7.88 (s, 1H); 8.20 (d, 1H); 9.00 (bs, 1H).
MS (m/z): 349 (M+).

The following compounds of Formula V identified in Table I are prepared analogously.



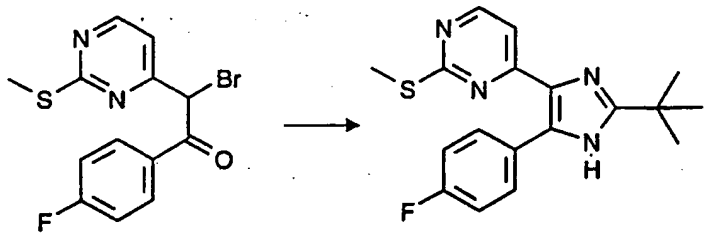
V

Table 1

Example No	Rx	Yield %	NMR/MS
2		66	1H-NMR (360 MHz DMSO-d6, 120 C): 7.05 (bd, 1H); 7.15 (t, 2H); 7.52-7.60 (bs, 1H); 7.68-7.70 (dd, 2H); 7.78 (s, 1H); 7.82 (bs, 1H); 8.40 (d, 2H); 8.90 (bs, 1H). MS (m/z): 410 (M+)
3		22	1H-NMR (400 MHz DMSO-d6, 120 C): 6.38 (dd, 1H); 6.90 (t, 1H); 7.05 (dd, 1H); 7.10 (t, 2H); 7.70 (dd, 2H); 7.78 (s, 1H); 8.35 (d, 2H); 8.60 (bs, 1H). MS (m/z): 346 (M-H+); 347 (M+)
4		10	1H-NMR (400 MHz DMSO-d6, 120 C): 7.10 (t, 3H); 7.20 (d, 2H); 7.42 (d, 2H); 7.62 (dd, 2H); 7.78 (s, 1H); 8.39 (d, 2H); 8.90 (bs, 1H). MS (m/z): 409 (M-H+); 410 (M+)
5		44	1H-NMR (400 MHz DMSO-d6, 120 C): 3.70 (s, 3H); 6.44 (dd, 2H); 7.00 (t, 1H); 7.05-7.15 (m, 2H); 7.22 (bs, 1H); 7.65 (dd, 2H); 7.78 (s, 1H); 8.39 (dd, 2H); 8.75 (bs, 1H). MS (m/z): 346 (M-H+); 347 (M+)
6		69	1H-NMR (360 MHz DMSO-d6, 120 C): 2.15 (s, 3H); 6.68 (bd, 1H); 6.90 (bm, 2H); 7.18 (t, 2H); 7.2-7.4 (bm, 2H); 7.68 (dd, 2H); 7.89 (s, 1H); 8.43 (d, 2H); 9.25 (bs, 1H). MS (m/z): 344 (M-H+); 345 (M+)
7		75	1H-NMR (400 MHz DMSO-d6, 120 C): 7.10 (t, 2H); 7.15 (d, 1H); 7.23 (bt, 1H); 7.65 (dd, 2H); 7.78 (s, 1H); 7.83 (bd, 1H); 7.92 (bs, 1H); 8.42 (d, 2H); 9.18 (bs, 1H). FAB-MS (m/z): 400 (MH+)

Example 8: 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-2-tert.butyl-4-pyrimidinyl) -1-H-imidazole

a) 4-(4-Fluorophenyl)-5-(2-methylthio-4-pyrimidinyl)-2-tert.butyl-1-H-imidazole

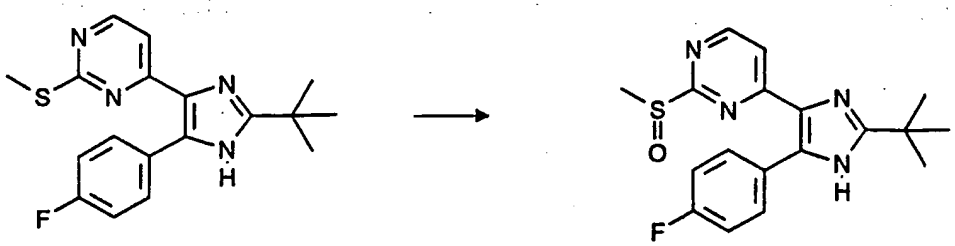


Pivalic acid (60 g, 538mmol) is melted by heating to 160 C. $(NH4)_2CO_3$ (5 g, 52.7 mmol) is added portionwise and after completed addition the mixture is cooled to 80 C. 4-Fluoro-2-bromo-2-(2-methylthio-4-pyrimidinyl)acetophenone (3 g, 3.8 mmol), dissolved in ca 1g of pivalic acid, is added and the reaction mixture heated to 180 C for 10 min., poured on a saturated solution of Na_2CO_3 and extracted with tert.butylmethylether. The organic phase is washed with 2N HCl and the water phase made basic with a saturated solution of Na_2CO_3 and extracted with tert.butylmethylether. Purification by silica gel chromatography (ethyl acetate/hexane 15/85 to 20/80) yields the title compound as yellow crystals (762mg, 25%).

1H-NMR (360 MHz, CDCl3): 1.50 (s, 9H); 2.62 (s, 3H); 6.92 (d, 1H); 7.15 (dd, 2H); 7.58 (dd, 2H); 8.27 (d, 2H), 9.91 (bs, 1H).

MS (m/z): 343 (MH+).

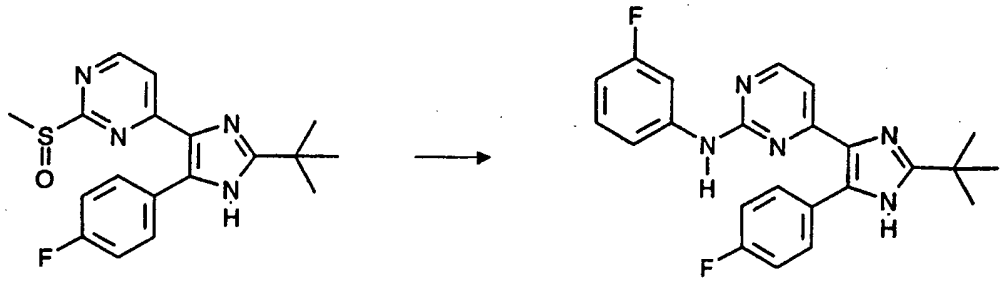
b) 4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-2-tert.butyl-1-H-imidazole



4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-2-tert.butylimidazole (0.4 g; 1.16 mmol) in methylene chloride (4 ml) is stirred and cooled to 5-10 C and mCPBA (55%, 0.48 g; 1.5 mmol) in methylene chloride (3 ml) added. After stirring at r.t. for 2 h, the reaction mixture is diluted with

ethyl acetate (30 ml) and washed once with 0.5N $Na_2S_2O_3$ (30 ml) and then twice with 1N NaOH. The organic phase is dried over Na_2SO_4 and evaporated to dryness to yield the title compound as light yellow crystals (397 mg, 95%), which are used without further purification.

c) 4-(4-Fluorophenyl)-5-(2-(3-fluorophenylamino)-4-pyrimidinyl)-2-tert.butyl-1-H-imidazole

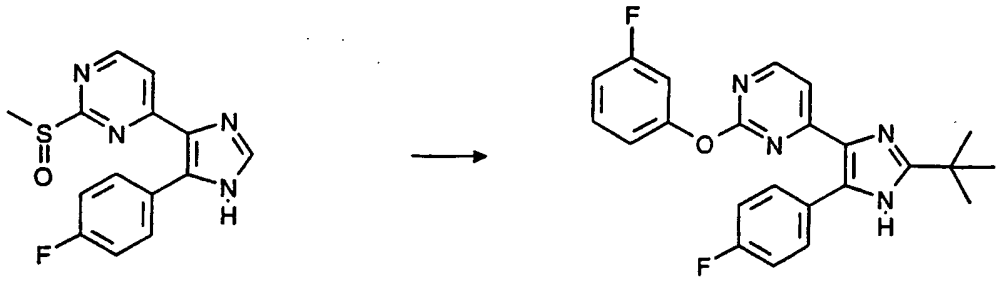


4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)-2-tert.butylimidazole (0.2 g, 0.55 mmol), 3-fluoroaniline (1 ml, 10 mmol) and $BF_3.OEt_2$ (0.07ml, 0.5 mmol) are heated for 20 min. at 160 C. The reaction mixture is diluted with tert.butylmethylether and washed with a solution of saturated Na_2CO_3. The organic phase is dried over Na_2SO_4, evaporated to dryness and the the product purified over silica gel (acetone/hexane 3/7) to yield the title compound, which is recrystallised from methanol (181 mg, 80%).

1H-NMR (400 MHz, DMSO-d6, 120 C): 1.50 (s, 9H); 6.60 (bs, 1H); 7.09 (dd, 2H); 7.15-7.30 (bs, 2H); 7.30-7.50 (bs, 2H); 6.05 (bs, 2H); 8.39 (bs, 2H); 11.60-11.70 (bs, 1-2H).

MS (m/z): 405 (M+), 390 (M-CH3).

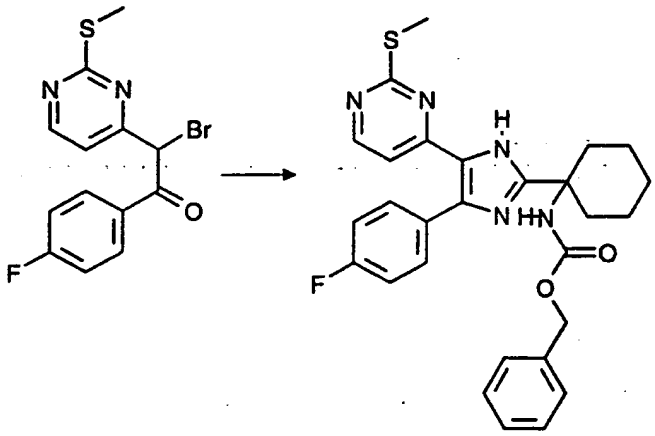
Example 9 **4-(4-Fluorophenyl)-5-(2-(3-fluorophenyloxy)-4-pyrimidinyl) -1-H-imidazole**



3-Fluorophenol (0.074 ml, 0.8 mmol) is added to a solution of $KN(TMS)_2$ (0.88 ml of a 1.3 M solution in toluene; 0.66 mmol) in THF (3 ml) and is stirred for 5 min. 4-(4-Fluorophenyl)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole (0.05 g, 0.16 mmol) is dissolved in warm THF (4 ml) and added rapidly to the reaction mixture, which is then stirred over night at room temperature. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, evaporated to dryness, and the product purified over silica gel (acetone/hexane 3/7 to 6/4) to yield the title compound (45 mg, 79%) as white crystals.
1H-NMR (360 MHz, DMSO-d6): 6.95 (d, 1H); 7.05 (dd(=t), 2H); 7.37 (dd, 1H); 7.56 (d, 1H); 7.58 (d, 1H); 7.85 (s, 1H); 8.55 (dd, 1H).
MS (m/z): 350 (M+), 349 (M-H).

Example 10 **2-(1-Aminocyclohexyl)-4-(4-fluorophenyl)-5-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole**

a) 5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-methylthio-4-pyrimidinyl)-1-H-imidazole

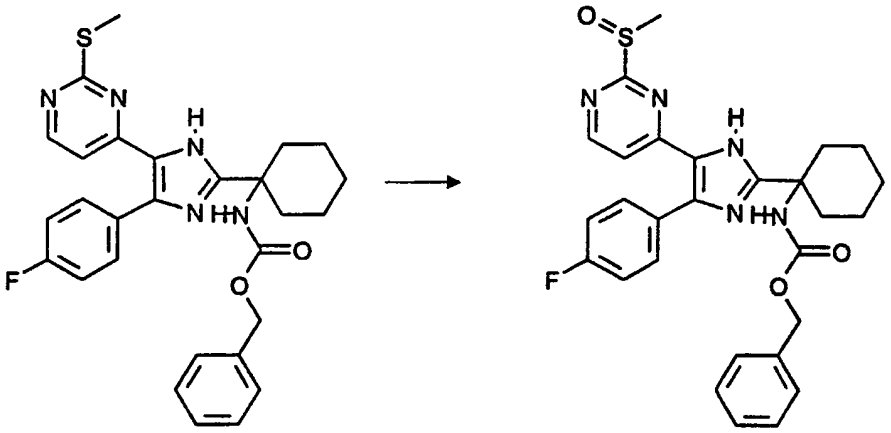


1-N-carbobenzyloxy-1-cyclohexanecarboxylic acid (E.Didier et al. Tetrahedron 1992, 48(39), 8471) (4.17g; 15mmol), and ammoniumcarbonate (Fluka; 1.46g; 15mmol) are dissolved in DMF (15ml) and heated to 110°C for 20min. until gas evolution ceases. After cooling to room temperature, 4-fluoro-2-bromo-2-(2-methylthio-4-pyrimidinyl)acetophenone (361mg; 1mmol) is added as a solid and the mixture heated to125°C for 2h. The reaction mixture is poured on 1M Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and chromatographed (SiO2; acetone/hexane 15/85) to give the pure title compound as a yellow oil (0.26g; 51%).

1H-NMR (400MHz; DMSO-d6): Mixture of tautomers: 1.30-1.65 (m, 8H); 2.06 (s, 3H); 2.15-2.30 (m, 2H); 4.95 (bd, 2H); 5.18 (t, 1H); 7.18-7.40 (m, 9H); 7.50 (d, 1H); 8.48 (d, 0.8H); 8.51 (d, 0.2H).

MS (m/z): 517 (M+).

b) 5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-methylsulfinyl-4-pyrimidinyl)-1-H-imidazole

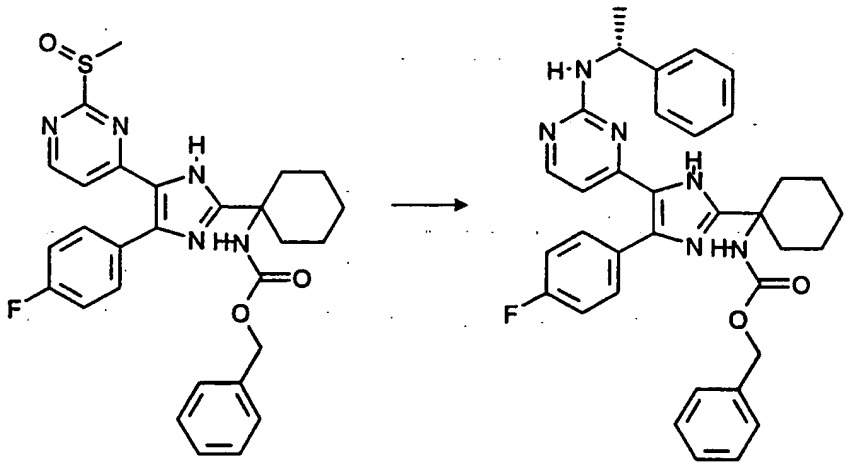


5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-methylthio-4-pyrimidinyl)imidazole (8.5g; 16.4mmol) is dissolved in methylene chloride (160ml) and cooled to 5°C under stirring, while mCPBA (4.46g; 21.86mmol) in methylene chloride (45ml) is added within 30min. After stirring for 15min., the reaction mixture is poured on 1M Na_2CO_3 and extracted twice with methylene chloride. The combined organic phases are dried over Na_2SO_4, evaporated to dryness and purified by chromatography (SiO_2; acetone/hexane 15/85) to yield the title compound as a yellow foam (5.6g; 62%).

1H-NMR (400MHz; DMSO-d6): Mixture of tautomers: 1.30-1.70 (m, 6H); 2.00-2.30 (m, 4H); 2.62 (s, 3H); 5.00 (s, 2H); 7.20-7.45 (m, 7H); 7.65-7.77 (m, 2H); 7.90 (d, 1H); 8.85 (d, 0.8H); 8.87 (d, 0.2H)

MS (m/z): 532.2 (M-H).

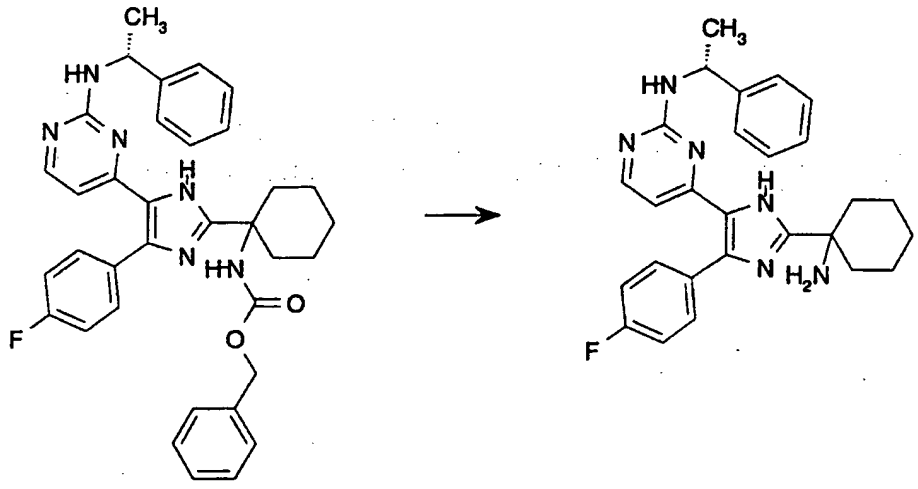
c) 5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole



5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-methylsulfinyl-4-pyrimidinyl)imidazole (2g; 3.75mmol) and R(+)-1-phenylethylamine (2.27ml; 18.75mmol) are dissolved in toluene (75ml) and heated to 125°C for 48h. Toluene is evaporated and the residue chromatographed (SiO_2; acetone/cycohexane 15/85) to yield the title compound as light yellow foam (1.6g; 72%).

MS (m/z): 591.3 (MH+).

d) 4-(4-Fluorophenyl)-2-(1-aminocyclohexyl)-5-(2-(R-1-phenylethylamino)-4-pyrimidinyl)-1-H-imidazole



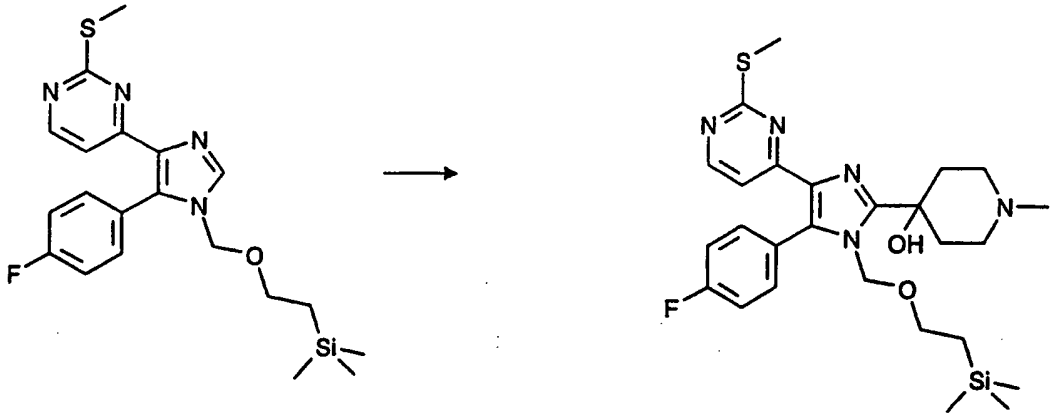
5-(4-Fluorophenyl)-2-(1-N-carbobenzyloxycyclohexyl)-4-(2-(R-1-phenylethylamino)-4-pyrimidinyl)imidazole (1g; 1.7mmol) is dissolved in HOAc (60ml) and HBr/HOAc (33%; 6ml) added. The reaction mixture is stirred at 35°C for 90min. and then poured on water (500ml) and washed twice with ether. The water phase is made basic with a saturated solution of Na_2CO_3 and 2N NaOH and extracted with tert. butyl methyl ether three times. The combined organic phases are washed with water, dried over Na_2SO_4, evaporated to dryness and chromatographed (SiO_2; TBME/MeOH/NH_3conc. 96/4/0.4) to yield the title compound as a white foam, which is cystallised from ether (574mg; 75%).

1H-NMR (400MHz; DMSO-d6, 120°C): 1.42 (d, 3H); 1.50-1.80 (m, 8H); 2.10 (bt, 2H); 5.00 (dq, 1H); 6.58 (d, 1H); 6.85 (d, 1H); 7.10-7.20 (m, 2H); 7.22-7.32 (m, 5H); 7.65-7.71 (m, 2H); 8.15 (d, 1H).

MS (m/z): 457 (MH+).

Example 11 **5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-phenylethylamino-4-pyrimidinyl)-1-H- imidazole**

a) 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylthio-4-pyrimidinyl)-1-(trimethylsilylethyloxymethyl)imidazole

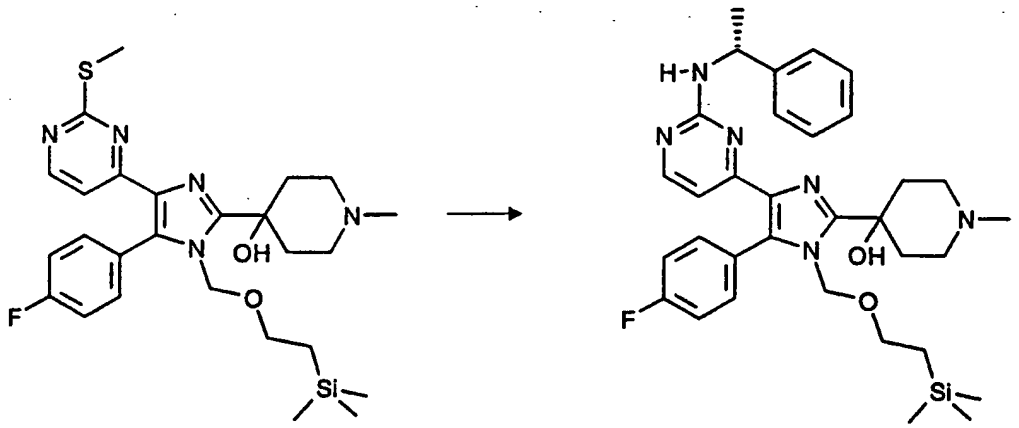


5-(4-Fluorophenyl)- 4-(2-methylthio-4-pyrimidinyl)-1-(trimethylsilylethyloxymethyl) imidazole (7.1g; 17mmol) is dissolved in THF (80ml) and cooled to -78°C. n-BuLi (12.7ml of a 1.6M solution; 20mmol) is added and the reaction stirred for 10min at -78°C. N-methyl-4-piperidone (2.6g; 22mmol) is added rapidly and after stirring for 5 minutes at -78°C, the reaction mixture is poured on a saturated solution of NaCl and extracted 3x with ethyl acetate. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to render the crude

product, which is purified by silica gel chromatography (tert.butyl methyl ether/methanol/NH_3 conc 97:3:0.2) to yield the title compund as yellow solid (5.35g; 59%).

1H-NMR (200 MHZ; CDCl3): 0.00 (s, 9H); 0.82 (dd, 2H); 1.97 (s, 3H); 1.98-2.10 (bd, 2H); 2.40 (s, 3H); 2.47-2.61 (m, 4H); 2.70-2.88 (m, 2H); 3.33 (dd, 2H); 5.30 (s, 2H); 7.20 (dd, 2H); 7.43 (dd, 2H); 7.65 (d, 1H); 8.42 (d, 1H).

b) 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-(trimethylsilylethyloxymethyl)imidazole

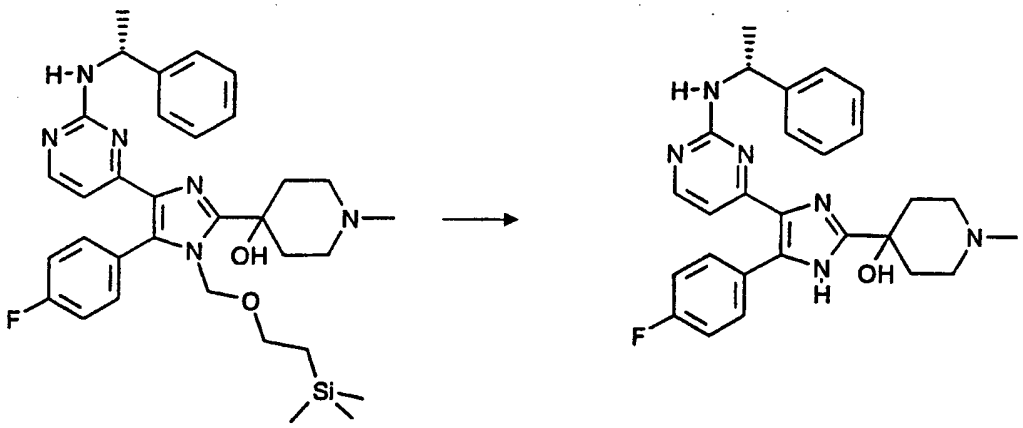


5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylthio-4-pyrimidinyl)-1-(trimethylsilylethyloxymethyl)imidazole (32.7 g; 0.06 mol) was dissolved in methylene chloride (200 ml), HOAc (50 ml) added and cooled to 0^0 C. mCPBA (19 g; 70%, 0.077 mol) in methylene chloride (120 ml) was added dropwise within 5 min. After stirring for another 5 min. the reaction mixture was poured on a saturated solution of Na2CO3 and extracted with ethyl acetate three times. The combined organic phases were dried over Na2SO4 and evaporated to dryness to render the crude product, which was filtered through silica gel (TBME/MeOH/NH3conc. 80/20/3). The solid product was washed with TBME and yielded pure 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylsulfinyl-4-pyrimidinyl)-1-(trimethylsilylethyloxymethyl)imidazole (24.2 g; 72%).

5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-methylsulfinyl-4-pyrimidinyl)-1-(trimethylsilylethyloxymethyl)imidazole (2.1g; 3.8mmol), R(+)-1-phenylethylamine (25ml) and toluene (25 ml) are heated to 140^0C for 2h. Toluene and excess R(+)-1-phenylethylamine are distilled off at 0.1 mm Hg and the residue purified by silica gel chromatography (acetone/methanol 90/10 to 95/5) to deliver 1.1g (47%) of the title compound as colorless crystals.

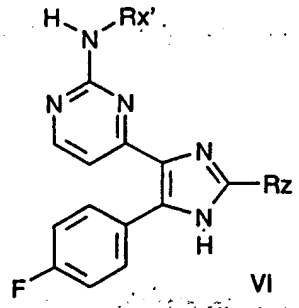
1H-NMR (360MHZ; DMSO-d6): -0.06 (s, 9H); 0.72 (bt, 2H); 1.16 (bs, 3H); 1.93-2.03 (m, 2H); 2.20 (s, 3H); 2.16-2.28 (m, 2H); 2.36 (bt, 2H); 2.53 (bt, 2H); 3.19-3.27 (m, 2H); 4.18-4.35 (bs, 1H); 5.30-5.43 (dd, 2H); 5.48 (s, 1H; OH); 6.97-7.05 (bs, 1H); 7.06-7.18 (m, 4H); 7.21-7.26 (t, 2H); 7.29-7.34 (t, 2H); 7.50-7.56 (t, 2H); 8.17 (d, 1H).
FAB-MS (m/z): 603 (MH+)

c) 5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-phenylethylamino-4-pyrimidinyl)-1-H- imidazole



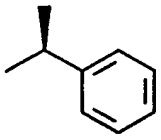
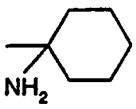
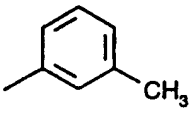
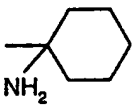
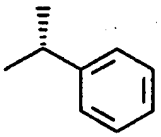
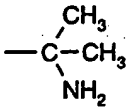
5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-(trimethylsilylethyloxymethyl)imidazole (740mg, 1.23mmol) is dissolved on EtOH (10ml) and hydrochloric acid (aqueous, 37%, 10ml) and kept at room temperature for 20 minutes. The reaction mixture is then poured on a saturated solution of Na_2CO_3 and extracted with ethyl acetate. The resulting yellow foam is triturated with tert.butyl methyl ether/diethyl ether and the solid obtained is filtered off to provide the title compound (514mg; 88.7%) as yellow powder.
1H-NMR (400MHz; DMSO-d6; 120°C): 1.3-1.52 (bm, 3H); 1.85 (bd, 2H); 2.15-2.30 (m, 2H); 2.25 (s, 3H); 2.43-2.61 (m, 4H); 4.5 (bs, 1H); 7.10-7.45 (m, 8H); 7.66 (dd, 2H); 8.15 (d, 1H).
FAB-MS (m/z): 473 (MH+, 100); 453 (25); 308 (45).

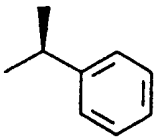
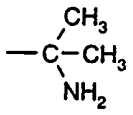
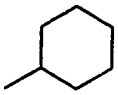
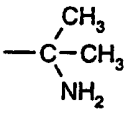
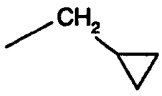
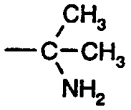
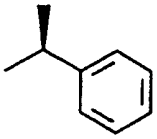
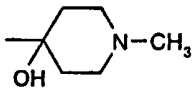
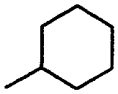
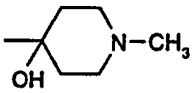
The compounds of Examples 12-17 of Formula VI identified in Table 2 below are prepared by analogy with Example 10 and similarly the compounds of Examples 18-26, also of formula VI and as identified in Table 2, are prepared by analogy with Example 11.

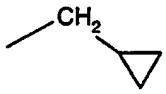
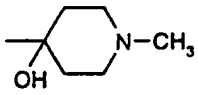
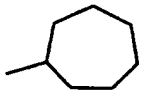
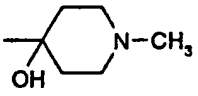
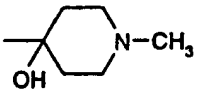


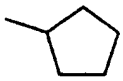
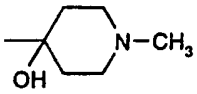
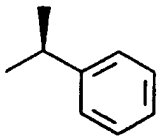
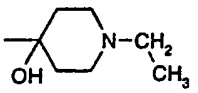
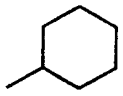
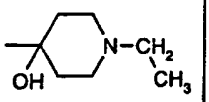
VI

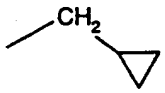
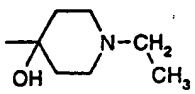
Table 2

Example No	Rx'	Rz	NMR/MS
12			NMR as Example 10 MS (m/z) ESI: 457 (MH+, 100)
13			1H-NMR (400MHz; DMSO-d6): 1.25-1.77 (m, 10H); 2.04 (bt, 2H); 2.15 (s, 3H); 6.65 (d, 1H); 6.91 (bt, 1H); 7.05 (bs, 1H); 7.17 (t, 2H); 7.26 (bd, 1H); 7.38 (bs, 1H); 7.63 (dd, 2H); 8.38 (d, 1H); 9.27 (bs, 1H). MS (m/z) EI: 442 (100); 425 (70); 413 (30); 399 (30).
14			1H-NMR (400MHz; $CDCl_3$): 1.61 (s, 9H); 1.71-1.98 (bs, 2H, NH2); 5.10 (bs, 1H); 5.53 (bs, 1H, NH); 6.55 (bs, 1H); 7.11 (bt, 2H); 7.26 (d, 1H); 7.38 (dd, 2H); 7.45 (bd, 2H); 7.56 (dd, 2H); 8.07 (d, 1H); 10.00 (bs, 1H, NH). MS (m/z) EI: 416 (M+, 10); 399 (100); 384 (90); 294 (30); 120 (30); 105 (50).

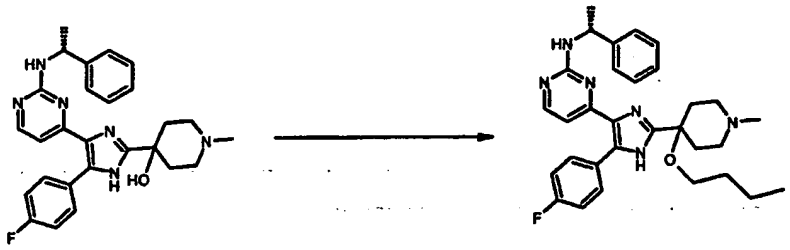
15			As for Example 14
16			1H-NMR (400MHz; DMSO-d6; 120° C).1.13-1.30 (m, 5H); 1.51 (s, 6H); 1.53-1.60 (m, 1H); 1.65-1.72 (m, 2H); 1.75-1.85 (m, 2H); 3.52-3.62 (m, 1H); 5.25 (s, 1H); 5.87 (s, 1H); 6.85 (d, 1H); 7.12-7.20 (m, 2H); 7.65-7.71 (m, 2H); 8.15 (s, 1H). MS (m/z) ESI: 395.2 (MH+).
17			1H-NMR (400MHz; DMSO-D6). Mixture of rotamers with broad signals: -0.06-0.13 (bs, 2H); 0.26-0.40 (bs, 2H); 0.72-0.97 (bs, 1H); 1.47 (s, 6H); 2.80-3.05 (bs, 2H, NH2); 3.13-3.45 (bm, 2H); 6.78-7.05 (bs, 2H); 7.22 (bt, 2H); 7.68 (bt, 2H); 8.17 (d, 1H); 12.00 (bs, 1H, NH).
18			as for Example 11
19			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 0.88-1.28 (m, 6H); 1.45-1.73 (m, 4H); 1.80-1.90 (m, 2H); 2.09-2.18 (bt, 2H); 2.19 (s, 3H); 2.32-2.45 (m, 2H); 2.46-2.52 (m, 2H); 2.60-2.70 (bs, 1H); 5.13 (bs, 0.7H); 5.25 (bs, 0.3H); 6.50 (bs, 1H); 6.85 (bd, 1H); 7.00 (bs, 1H); 7.13-7.27 (m, 2H); 7.55-7.70 (m, 2H); 8.18 (bt, 1H). MS (m/z) ESI: 449.2 (MH-, 100).

20			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 0.00 (bs, 1H); 0.13 (bs, 1H); 0.30 (bs, 1H); 0.38 (bs, 1H); 0.80 (bs, 0.7H); 0.95 (bs, 0.3H); 1.84 (bd, 2H); 2.13 (bt, 2H); 2.20 (s, 3H); 2.38 (bt, 2H); 2.49 (bd, 2H); 2.75 (bs, 2H); 3.05 (bs, 1H); 5.15 (bs, 0.7H); 5.27 (bs, 0.3H); 6.75 (bs, 1H); 7.05 (bs, 1H); 7.20 (bt, 2H); 7.65 (bs, 2H); 8.17 (d, 1H). MS (m/z) ESI: 421.2 (MH-, 100).
21			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 0.92-1.69 (m, 12H); 1.83 (bd, 2H); 2.12 (bt, 2H); 2.21 (s, 3H); 2.38 (bt, 2H); 2.50 (bd, 2H); 3.50-3.80 (bs, 1H); 5.15 (bs, 0.7H, OH); 5.26 (bs. 0.3H, OH); 6.58 (bs, 1H, NH); 6.89 (bd, 0.3H); 7.02 (bs, 0.7H); 7.23 (bt, 2H); 7.62 (bs, 2H); 8.18 (d, 1H). MS (m/z) EI: 464 (M+, 50); 446 (100); 72 (55).
22			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 0.30-0.68 (m, 4H); 1.85 (bd, 2H); 2.13 (bt, 2H); 2.20 (s, 3H); 2.38 (bt, 2H); 2.52 (bd, 2H); 2.65-2.80 (m, 1H); 5.17 (bs, 0.6H, OH); 5.26 (bs, 0.4H, OH); 6.71 (bs, 0.4H, NH); 6.95 (bs, 0.6H, NH); 7.08 (bs, 0.7H); 7.20 (bt, 2H); 7.26 (bs 0.3H); 7.78 (bt, 2H); 8.20 (bd, 1H). MS (m/z) EI: 408 (M+; 70); 390 (100); 338 (40); 295 (20); 72 (50).

23			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 1.12-1.71 (m, 8H); 1.85 (bd, 2H); 2.13 (bt, 2H); 2.19 (s, 3H); 2.38 (bt, 2H); 2.48 (bd, 2H); 3.51-3.78 (bs, 1H); 5.16 (bs, 0.7H, OH); 5.27 (bs, 0.3H, OH); 6.68 (bs, 1H); 6.95-7.08 (bd, 1H, NH); 7.71 (bt, 2H); 7.63 (bs, 2H); 8.17 (d, 1H). MS (m/z) EI: 436 (M+, 50); 418 (100); 366 (25); 72 (35).
24			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 1.03 (bt, 3H); 1.30 (bs, 2.1H); 1.42 (bs, 0.9H); 1.86 (bd, 2H); 2.12 (bt, 2H); 2.30-2.47 (m, 4H); 2.55 (bd, 2H); 4.63 (bs, 0.6H); 5.04 (bs, 0.4H); 5.14 (s, 0.7H, OH); 5.28 (s, 0.3H, OH); 6.68 (bs, 1H, NH); 7.03 (bs, 1H); 7.10-7.48 (m, 7H); 7.66 (bs, 2H); 8.18 (bd, 1H). MS (m/z) EI: 486 (M+, 40); 468 (100); 86 (35).
25			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 0.88-1.30 (m, 7H with sharp triplett at 1.03; (3H)); 1.45-1.73 (m, 6H); 1.85 (bd, 2H); 2.13 (bt, 2H); 2.29-2.47 (m, 4H with sharp quartett at 2.34 (2H)); 2.56 (bs, 2H); 3.06-3.28 (bs, 1H); 5.13 (s, 0.7H, OH); 5.23 (s, 0.3H, OH); 6.51 (bs, 0.6H, NH); 6.85 (bs, 0.4H, NH); 7.01 (bs, 1H); 7.22 (bt, 2H); 7.62 (bs, 2H); 8.17 (d, 1H). MS (m/z) EI: 464 (M+, 35); 446 (100), 86 (30).

26			1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: -0.10-0.45 (m, 4H); 0.65-0.91 (bs, 1H); 1.03 (t, 3H); 1.84 (bd, 2H); 2.12 (bt, 2H); 2.30-2.47 (m, 4H with quartett at 2.36 (2H)); 2.57 (bs, 2H); 2.65-2.90 (bs, 1H); 2.95-3.22 (bs, 1H); 5.15 (s, 0.7H, OH); 5.26 (s, 0.3H, OH); 6.77 (bs, 1H, NH); 7.08 (bs, 1H); 7.23 (bt, 2H); 7.65 (bs, 2H); 8.18 (d, 1H). MS (m/z) EI: 436 (M+, 70); 418 (100); 352 (30); 86 (10).

Example 27: 5-(4-Fluorophenyl)-2-(1-n-butyloxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole



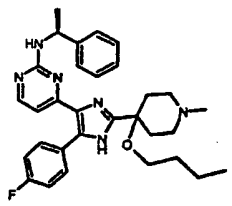
5-(4-Fluorophenyl)-2-(1-hydroxy-4-methylpiperidinyl)-4-(2-(R)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole (Example 11) (430 mg; 0.911 mmol), 1-butanol (30 ml) and H_2SO_4 (360 mg; 3.6 mmol) are refluxed for 4.5 h and evaporated to dryness. The residue is taken up in a saturated solution of Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered, evaporated and purified via SiO_2 chromatography (TBME/MeOH/NH_3 conc 98/2/0.2 to 96/4/0.2) to yield the title compound as colorless crystals (198 mg; 41%).

1H-NMR (400MHz; DMSO-d6). Mixture of rotamers with broad signals: 0.78-0.83 (m, 3H); 1.21-1.49 (m, 7H); 2.05-2.13 (bs, 4H); 2.17 (s, 3H); 2.25-2.48 (m, 4H); 3.05-3.16 (bq, 2H); 4.48-4.72 (bs, 0.6 H); 4.95-5.13 (bs, 0.4H); 6.90-7.10 (bs, 2H); 7.10-7.33 (m, 6H); 7.53-7.70 (m, 2H); 8.18 (d, 1H); 12.00 (bs, 1H, NH)); 13.00 (bs, 1H, NH).

MS (m/z) EI: 428 (M+; 20); 471 (55); 455 (100).

The compound of Example 28 is prepared by analogy with example 27 from the compound of Example 18.

Example 28: 5-(4-Fluorophenyl)-2-(1-n-butyloxy-4-methylpiperidinyl)-4-(2-(S)-1-phenylethylamino-4-pyrimidinyl)-1-H- imidazole



The title compound is the enantiomer of example 27. Their NMR- and MS-spectras are identical.

The Agents of the Invention, as defined above, e.g., of formula I, particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

In particular Agents of the Invention possess p38 MAP kinase (Mitogen Activated Protein Kinase) inhibiting activity. Thus the Agents of the Invention act to inhibit production of inflammatory cytokines, such as TNF-α and IL-1, and also to potentially block the effects of these cytokines on their target cells. These and other pharmacological activities of the Agents of the Invention as may be demonstrated in standard test methods for example as described below:

p38 MAP kinase Assay

The substrate (GST-ATF-2; a fusion protein comprising amino acids 1-109 of ATF-2 and the GST protein obtained by expression in E. coli) is coated onto the wells of microtiter plates (50 µl/well; 1 µg/ml in PBS/0.02% Na azide) overnight at 4 °C. The following day, the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide and are blocked with PBS/2% BSA/0.02% Na Azide for 1 h at 37 °C. Plates are washed again 4 times with PBS/0.5% Tween 20/0.02% Na azide. The kinase cascade reaction is then started by adding the following reactants in 10 µl aliquots to a final reaction volume of 50 µl.

1. Agents of the Invention titrated from 10 to 0.001 μM in 10-fold dilutions or solvent (DMSO) or H_2O.
2. Kinase buffer (5x); pH 7.4; 125 mM Hepes (Stock at 1M; Gibco #15630-056), 125 mM β-glycerophosphate (Sigma #G-6251):125 mM $MgCl_2$ (Merck #5833); 0.5 mM Sodium orthovanadate (Sigma #5-6508), 10 mM DTT (Boehringer Mannheim #708992). The (5x) kinase buffer must be prepared fresh the day of the assay from 5x stock solutions kept at RT. DTT is kept at -20 °C and is added as the last reagent.
3. His-p38 MAP kinase (10 ng/well; Novartis - a fusion protein comprising full length murine p38 MAP kinase and a His tag, obtained by expression in E. coli)
4. cold ATP (final concentration 120 μM; Sigma #A-9187)
5. Water

After 1h at 37 °C the kinase reaction is terminated by washing the plates four times as previously described. Phosphorylated GST-ATF-2 is then detected by adding:

1. the PhosphoPlus ATF-2 (Thr71) Antibody (50 μl/well; 1/1000 final dilution in PBS/2% BSA/0.02% Na Azide; New England Biolabs #9221L) for 90 min at RT.
2. Biotin labelled goat-anti-rabbit IgG (50 μl/well; 1/3000 final dilution in PBS/2% BSA/0.02% Na Azide; Sigma #B-9642) for 90 min at RT.
3. Streptavidin-alkaline phosphatase (50 μl/well; 1/5000 dilution in PBS/2% BSA/0.02% Na Azide; Jackson Immunoresearch #016-050-084) for 30 min at RT.
4. Substrate (100 μl/well; Sigma 104 Phosphatase substrate tablets, 5 mg/tablet; #104-105; 1 mg/ml in substrate buffer, Diethanolamine (97 ml/l; Merck #803116) + $MgCl_2.6H_20$ (100 mg/l; Merck #5833) + Na Azide (0.2 g/l) + HCl 1M to pH 9.8) 30 min at RT.

After step 1,2 and 3 the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide. After step 4, the plates are read in a Bio-Rad microplate reader in a dual wavelength mode (measurement filter 405 nm and reference filter 490 nm). The bachground value (without ATP) is subtracted and IC_{50} values are calculated using the Origin computer program (4 parameter logistic function).

Agents of the Invention typically have IC_{50}s for p38 MAP kinase inhibition in the range from about 100 nM to about 10 nM or less when tested in the above assay.

Assay for Inhibition of TNF-α release from hPBMCs

Human peripheral blood mononuclear cells (hPBMCs) are prepared from the peripheral blood of healthy volunteers using ficoll-hypaque density separation according to the method of Hansell et al., J. Imm. Methods (1991) 145: 105. and used at a concentration of 10^5 cells/well in RPMI 1640 plus 10% FCS. Cells are incubated with serial dilutions of the test compounds for 30 minutes at 37°C prior to the addition of IFNg (100 U/ml) and LPS (5 mg/ ml) and subsequently further incubated for three hours. Incubation is terminated by centrifugation at 1400 RPM for 10 min. TNF-α in the supernatant is measured using a commercial ELISA (Innotest hTNFa, available from Innogenetics N.V., Zwijnaarde, Belgium). Agents of the Invention are tested at concentrations of from 0 to 10 mM. Exemplified Agents of the Ivention typically suppress TNF release in this assay with an IC_{50} of from about 500 nM to about 50 nM or less when tested in this assay.

Assay for Inhibition of TNF-α Production in LPS stimulated mice

Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF-α) into the periphery. This model is be used to analyse prospective blockers of TNF release in vivo.

LPS (20 mg/kg) is injected i.v. into OF1 mice (female, 8 week old). One (1) hour later blood is withdrawn from the animals and TNF levels are analysed in the plasma by an ELISA method using an antibody to TNF-α. Using 20 mg/kg of LPS levels of up to 15 ng of TNF-α / ml plasma are usually induced. Compounds to be evaluated are given either orally or s.c. 1 to 4 hours prior to the LPS injection. Inhibition of LPS-induced TNF-release is taken as the readout.

Agents of the Invention typically inhibit TNF production to the extent of up to about 50% or more in the above assay when administered at 10 mg/kg p.o.

As indicated in the above assays Agents of the Invention are potent inhibitors of TNF-α release. Accordingly, the Novel Compounds have pharmaceutical utility as follows:

Agents of the Invention are useful for the prophylaxis and treatment of diseases or pathological conditions mediated by cytokines such as TNFα and IL-1, e.g., inflammatory

conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection, e.g. for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants and for the prevention of graft-versus-host disease, such as following bone marrow transplants.

Agents of the Invention are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Agents of the Invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways.

Agents of the Invention are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by TNF, especially by TNFa, e.g., acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe burns; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS -related cachexia, e.g., associated with or consequential to HIV infection.

Agents of the Invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides.

For the above indications the appropriate dosage will, of course, vary depending, for example, on the particular Agent of the Invention employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are obtained at daily dosages of from about 1 to about 10mg/kg/day p.o.. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 50 to about 750mg of Novel Compound administered orally once or, more suitably, in divided dosages two to four times/day.

The Novel Compounds may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Novel Compounds may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg Novel Compound per unit dosage.

In accordance with the foregoing the present invention also provides in a further series of embodiments:

A. A method of inhibiting production of soluble TNF, especially TNFα, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, or alleviating one or more symptoms of any of the above mentioned conditions.

B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or

treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

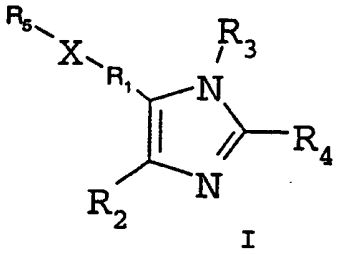
C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune of inflammatory disease or condition.

CLAIMS

1. A 4-phenyl-5-(2-aryl-X)-4-pyrimidinyl-, 4-phenyl-5-(2-cycloalkyl-X)-4-pyrimidinyl-, 4-phenyl-5-(2-aralkyl-X)-4-pyrimidinyl- or 4-phenyl-5-(2-cycloalkylalkyl-X)-4-pyrimidinyl-imidazole, in which the 5-pyrimidinyl substituent is aryl, cycloalkyl, aralkyl or cycloalkylalkyl substituted directly via a heteroatom X selected from N, O or S, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof..

2. A compound according to claim 1 of formula I



I

wherein

R_1 is pyrimidinyl;

X is $-NR_6-Y-$, -O- or -S-,

where R_6 is H, C_{1-4}alkyl, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, C_7-C_{19}aralkyl or C_4-C_{19}heteroaralkyl, and -Y- is C_{1-4}alkylene or a direct bond ;

R_2 is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF_3,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C_{1-4}alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C_{1-4}alkyl C_{1-4}alkylcarbonyl or C_{1-4}alkylthiocarbonyl substitued,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C_{1-10}alkoxy, C_{2-10}alkenoxy, C_{2-10}alkynoxy, C_{3-7}cyclalkoxy, C_{5-7}cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester,

optionally mono- or di-C_{1-4}alkyl-substituted-C_{0-1}alkyl optionally C_{1-4}alkyl- or C_{3-5} cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted-C_{1-4}alkoxy, C_{2-4}alkenoxy, C_{2-4}alkynoxy, C_{3-5}cycloalkoxy or C_{3-5}cyclothioalkoxy,

optionally halo substituted C_{1-4} alkyl,

oxycarbonyl or optionally N-C_{1-4}alkyl-substituted aminocarbonyl both of which are optionally C_{1-4}alkyl or C_{3-5}cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di-C_{1-4}alkyl-substituted-C_{0-1}alkylamine which is optionally mono-or di-N-C_{1-4} alkyl substituted,

optionally mono- or di-C_{1-4}alkyl-substituted-C_{0-1}alkyl optionally N-C_{1-4}alkyl-substituted amino-carbonyl or -thiocarbonyl,

optionally N-C_{1-4}alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C_{1-4}alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_{1-4}alkyl C_{1-4}alkylcarbonyl or C_{1-4}alkylthiocarbonyl substitued, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C_{1-4}alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl,

optionally mono- or di-N-C_{1-4}alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_{1-4}alkyl C_{1-4}alkylcarbonyl or C_{1-4}alkylthiocarbonyl substitued;

R_3 is hydrogen,

heterocyclyl,

heterocyclylC_{1-10}alkyl,

optionally halo substituted C_{1-10}alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10}alkyl, heteroaryl, or heteroarylC_{1-10}alkyl,

optionally mono-or di-C_{1-4}alkyl-substitutedC_{0-10}alkyl-oxycarbonyl or -oxythiocarbonyl optionally substituted by C_{1-10}alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10}alkyl, or

optionally mono-or di-C_{1-4}alkyl-substitutedC_{1-10}alkyl

-cyano,

-nitro,

-hydroxy, -C_{1-10}alkoxy, -C_{3-7}cycloalkoxy, -heterocycloxy, -heterocyclylC_{1-10}alkoxy, -aryloxy, -arylC_{1-10}alkoxy, -heteroaryloxy, -heteroarylC_{1-10}alkoxy (and thio oxy analogues thereof),

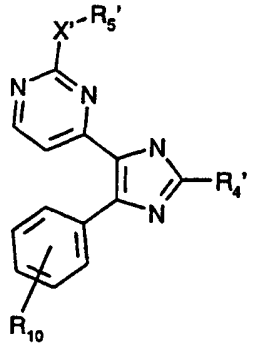
optionally substituted amino, carboxylate, thiocarboxylate, carbonyl or thiocarbonyl, sulphinyl or sulphonyl;

R_4 is H, or C_{1-10}alkyl, C_{3-10}cycloalkyl, C_{3-18}heterocycloalkyl, C_{6-18}aryl, or C_{3-18}heteroaryl all optionally substituted by up to 4 substituents separately selected from alkyl, halogen, halo-substitued-alkyl, hydroxy, alkoxy, alkylthio, or optionally substituted amino;

R_5 is C_6-C_{18}aryl, C_3-C_{18}heteroaryl, or C_3-C_{12}cycloalkyl optionally substituted by up to 3 substituents separately selected from alkyl, halogen, halo-substitued-alkyl, hydroxy, alkoxy, alkylthio, optionally substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

3. A compound according to claim 1 of formula I'



I'

wherein

R_5' is phenyl or C_3-C_7cycloalkyl each of which is optionally mono-substituted by halogen, C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, trihalomethyl or -NR_7R_8, where R_7 and R_8 are idependently H, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}heteroaryl, C_{7-11}aralkyl or C_{7-11}heteroaralkyl;

R_{10} is halogen, cyano, amido, thioamido, amino or C_{1-6}alkyl;

R_4' is H, C_{1-6}alkyl, 1-hydroxyC_{1-10}alkyl, 1-C_{1-6}alkoxyC_{1-10}alkyl, 1-aminoC_{1-10}alkyl, 1-hydroxyC_{3-10}cycloalkyl, 1-C_{1-6}alkoxyC_{3-10}cycloalkyl, 1-aminoC_{3-10}cycloalkyl, 1-hydroxyC_{3-18}heterocycloalkyl, or 1-C_{1-6}alkoxyC_{3-18}heterocycloalkyl, and

X' is -NH-Y'-, -O- or -S-, where Y' is -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$- or a direct bond,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

4. A compound according to claim 1 as described in any one of Examples 1 to 28.

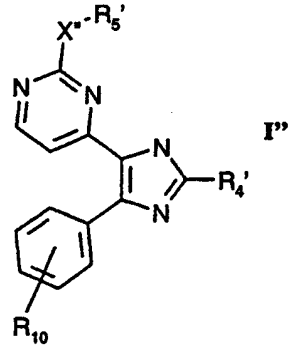
5. A method of inhibiting production of soluble TNF, especially TNFα, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of a compound according to claim 1.

6. A compound according to claim 1 for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

7. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

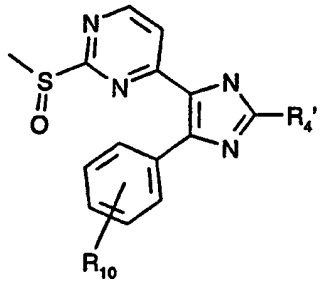
8. Use of a compound according to claim 1 in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

9. A process for the preparation of a compound of formula I''



I''

wherein R_4', R_5' and R_{10} are as defined in claim 3 and X'' is -NH- or -O-, which comprises reacting the corresponding precursor compound of formula II



II

wherein R_4' and R_{10} are as defined in claim 3, with the corresponding R_5'-NH_2 or R_5'-OH derivative.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 99/08358

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/04 C07D401/14 A61K31/505 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 47618 A (BILODEAU MARK T ;BUTCHER JOHN W (US); MERCK & CO INC (US); CLAREMO) 18 December 1997 (1997-12-18) the whole document	1-9
X	WO 97 25045 A (SMITHKLINE BEECHAM CORP ;ADAMS JERRY L (US); BOEHM JEFFREY C (US);) 17 July 1997 (1997-07-17) claims 1,14	1-9
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2000	29/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

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Int. ional Application No
PCT/EP 99/08358

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